CONNOX

University of North Carolina, Chapel Hill
Committee on the Protection of the Rights of Human Subjects (Medical IRB)

APPLICATION FOR APPROVAL OF RESEARCH INVOLVING HUMAN SUBJECTS

TE: May 6, 2004 **IRB STUDY NUMBER (leave blank if new submission)**: 00-CEMLB-476

TITLE OF STUDY: Physiological Changes in Healthy Young Adults Exposed to Concentrated Chapel Hill Ambient Air Particles and Nitrogen Oxides

NAME AND DEGREE(S) OF PRINCIPAL INVESTIGATOR: Yuh-Chin T. Huang, MD **DEPT**: Center for Environmental Medicine, Asthma and Lung Biology; Human Studies Division, US EPA
PID NUMBER OF PRINCIPAL INVESTIGATOR: 7103-45475
MAILING ADDRESS:CB#7310, 104 Mason Farm Road
Chapel Hill, NC 27599-7310
PHONE: 919-843-9504 **FAX**: 919-966-6271 **PAGER**: 919-216-6008
E-MAIL: Huang.Tony@epa.gov

NAMES AND DEGREE(S) OF CO-INVESTIGATORS: Robert Devlin, Ph.D, Philip Bromberg, MD, Andy Ghio, MD, Wayne Cascio, MD, Martha Almond, RRT, RPFT
NAME AND PHONE NUMBER OF RESEARCH COORDINATOR, IF APPLICABLE: NA

NAME OF FUNDING SOURCE: United States Environmental Protection Agency

I. Agreements

Principal Investigator:
I certify that each of the above-named co-investigators has accepted his/her role in this study. I agree to a continuing exchange of information with the Committee on the Protection of the Rights of Human Subjects (IRB). I agree to obtain IRB approval before making any changes or additions to the project. I will provide progress reports at least annually, or as requested. I agree to report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. A copy of the consent form will be given to each subject and the signed original will be retained in my files. If the study involves treatment of UNC Hospitals patients, a copy of the consent form will be placed in each subject's medical record.

Signature of Principal Investigator — Date: 5/11/04

Signature of Faculty Advisor if P.I. trainee or Non-Faculty — Date

Department Chair of P.I. (or Vice-Chair if Chair is investigator or otherwise unable to review):
I have reviewed this research study. I believe the research is sound, that the study design and methods are adequate to achieve the study goals, and that there are appropriate resources (financial and otherwise) available to the investigator. I support it, and hereby submit it for further review.

Signature of Department Chair — Department — Date

(rev. 03/19/01)

II. Summary Checklist

ARE THE FOLLOWING INVOLVED?	YES	NO
Surveys, questionnaires or interviews *If research is limited to use of surveys, questionnaires or interviews, Submit **Exemption Application Form** instead of this application.*	☐	☒
Existing Patient Records and/or Specimens *If research is limited to study of existing medical records and /or samples, Submit **Short Form** instead of this application.*	☐	☒
Investigational Drug(s) **IND#** *If "yes", do you intend to use the UNC Hospitals Investigational Drug Service?*	☐ ☐	☒ ☐
Approved drugs for "non-FDA-approved" conditions	☐	☒
Placebo(s)	☐	☒
Experimental devices, instruments, machines **IDE#**	☐	☒
Genetic studies on subjects' specimens	☐	☒
Storage of subjects' specimens for future, as-yet-undesignated research *If "yes", see **Instructions for Submitting IRB Applications for Research that Includes the Storage of Human Biologic Specimens**.*	☐	☒
Fetal tissue	☐	☒
Videotaping, audiotaping, filming of subjects	☐	☒
Non-patient volunteers	☒	☐
Patients as subjects	☐	☒
Minors (less that 18 years old) *If "yes", indicate:* **Age range to years**	☐	☒
Do you intend to target your enrollment at: -Students or staff as subjects?	☒	☐
-Non-English-speaking subjects?	☐	☒
-Decisionally impaired or mentally incompetent subjects?	☐	☒
-Prisoners, parolees and other convicted offenders as subjects?	☐	☒
-Pregnant subjects?	☐	☒
Will HIV tests be performed?	☐	☒
Will subjects be studied at off-campus sites?	☐	☒
Is this a multicenter study? *If "yes", is UNC-CH the sponsor or coordinating center?*	☐ ☐	☒ ☐
Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise *If "yes", approval by the Radiation Safety Committee is required.*	☐	☒
Recombinant DNA or gene transfer to human subjects *If "yes", approval by the Biologic Safety Committee is required.*	☐	☒
Is this an oncology study? *If "yes", submit this application directly to the Oncology Protocol Review Committee.*	☐	☒
Will subjects be studied in the General Clinical Research Center? *If "yes", obtain GCRC Addendum from the GCRC and submit complete application (IRB application and Addendum) to the GCRC.*	☐	☒

III. Required Education in Human Subjects Protection

UNC policy requires that all persons engaged in research involving human subjects must complete training in hical conduct of research and protection of subjects. This applies to all research, regardless of funding source. further information, including what options are acceptable in fulfillment of these requirements, see nttp://www.med.unc.edu/irb/Education2.htm

Individuals who have completed training should have been entered into the Human Subjects Training Database maintained by the Office of Research Services (ORS). To print documentation, visit http://zeppo.admin.unc.edu/isapi/certweb.dll and enter the names of each individual involved with this research project. Names not returned by the database are not recognized as having satisfied the education requirement. For questions regarding the database, please contact ORS at 962-7757.

WITH THIS APPLICATION, please submit the printout from the ORS database, verifying that each individual involved in the research (including faculty, staff, students and outside collaborators, if responsible to this IRB) has satisfied the education requirements.

IV. Potential Conflict of Interest

The following questions apply to any investigators or study staff involved with industry-sponsored research, and/or their immediate family members (spouse, dependent children, others). Within the past 12 months or the next 12 months, have you or will you:

ceive any form of personal compensation from the Sponsor, luding salary, consulting fees, honoraria, royalties, equipment, etc.?	☐ YES	☒ NO
If so, does or will that compensation exceed $10,000?	☐ YES	☒ NO
Have an ownership interest of any nature in the Sponsor or product under study, including equity, stock options, etc.?	☐ YES	☒ NO
If so, does or will that interest exceed $10,000 in value?	☐ YES	☒ NO
If so, does that interest represent more than 5% ownership in the Sponsor?	☐ YES	☒ NO
Hold any position with the Sponsor, including officer, director, trustee, consultant, member of advisory board, etc.?	☐ YES	☒ NO
Have an intellectual property interest on any technology or invention used in this study, including patent rights, copyright, etc.?	☐ YES	☒ NO
Have a conflict of interest disclosed through the University's annual evaluation policy that relates to this research study?	☐ YES	☒ NO

If the answer is "YES" to any of the questions above, please include an explanation with this application. As h any changes to the research itself, relationships or interests that develop later should be brought to the B's attention for further consideration.

V. Description of Proposed Research Activity

Entire application should not usually exceed 5 single-spaced pages using a 12-point font.

Purpose and Rationale: Provide a brief summary of the background information, state the research question(s), and tell why the study is needed. Avoid an extensive literature review.

During the past decade, several epidemiological studies have reported statistically significant positive correlations between daily concentrations of ambient air particles and acutely increased mortality and morbidity. It has been estimated that 50,000 - 60,000 excess deaths in the U.S. each year may be attributable to ambient particles. Several panel studies have reported associations between fine PM and decreased heart rate variability and increased vascular markers of inflammation. In addition, recent controlled human exposure studies have reported that fine particles can increase,pulmonary inflammation, decrease heart rate variability, and increase vascular factors of inflammation and blood coagulation. However, these latter studies only assessed the effects of particulate matter. In the real world, people are simultaneously exposed to both gaseous pollutants (e.g. ozone, nitrogen dioxide) and particles. Recognition of this lead the National Research Council to list studies of PM and gaseous co-pollutants as one of the ten highest priorities in PM research.

One of these copollutants that frequently occurs together with PM is nitrogen oxides (**NOx**), which are produced during combustion processes. NOx-concentrations may reach values over 1 ppm NO and 0.5 ppm NO_2, especially during smog situations. NOx consists of nitric oxide (NO) and nitrogen dioxide (NO_2). NO dominates near roadsides and peaks in morning rush hours while NO_2 levels show less temporal and spatial variability.

NO_2 is an oxidant capable of oxidizing and nitrating lipids and proteins and can cause cytotoxic effects on the cell membranes of epithelial cells as well as macrophages. Controlled exposure of healthy humans to 2 ppm NO_2 reduced phagocytic capacity in macrophages. At similar concentrations controlled NO_2 exposure produced small changes in large airway function and increased air way reactivity to methacholine. **NO** is an endogenously produced mediator which regulates tone of smooth muscles and thereby regulates vascular function. NO also modulates neutrophil chemotaxis, adherence and activation. NO when given by inhalation produced selective pulmonary vasodilatation, thus increased pulmonary vascular blood flow. In a recent study in healthy volunteers, exposure to 0.2 ppm NO during exercise and breathing cold air was found to reduce forced vital capacity and forced expiratory volume in 1 second, which was attributed to the changes in vascular function. The inflammatory effects of NO_2 and vascular effects of NO may thus enhance the adverse effects of PM.

In this study we hypothesize that NO2 and PM2.5 synergistically affect the cardiopulmonary system beyond what either pollutant is capable of inducing by itself. Cardiopulmonay impairment will be assessed by measuring changes in bronchoalveolar lavage (BAL) neutrophils, decreases in heart rate variability, and changes in blood factors involved in inflammation and coagulation.

2. **Subjects:** Specify number, age, gender, ethnicity, and whether healthy volunteers or patients. If patients, specify the disease or condition and indicate how potential subjects will be identified. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided. NIH applications require that women, minorities, and children be included or that their exclusion be justified. If children are involved, refer to "Children as Research Subjects".

Subjects will be healthy volunteers aged between 18 and 40. We will make every effort to include both genders and minorities. Pregnant women will be excluded since the possible effects of NOx and PM2.5 on the fetus are unclear. (You will need to include a power calculation here, per Roger Cortesi.) Indicate that BAL PMNs are the primary hypothesis, that the mean value of PMNs in air-exposed people is 1%, that we consider anything above 4% to be biologically relevant (and therefore are looking for a delta of 3%), that the standard deviation of PMN changes is 1.38; beta of 0.8, etc. etc. You should come out with an n between 10 and 12.)

3. **Inclusion/Exclusion criteria:** List required characteristics of potential subjects, and those that preclude enrollment.

To participate in this study, subjects have to be healthy and fulfill the following requirements:

- Non-smokers for at least 1 year prior to study and less than 5 pack-years in life
- No history of cardiac diseases and a normal resting ECG
- No active allergies or respiratory diseases to include: hay fever, dust allergies, rhinitis, asthma, chronic bronchitis, chronic obstructive pulmonary disease, tuberculosis, hemoptysis or recurrent pneumonia
- Not presently taking any medication including over the counter medication (except birth control pills)
- Not being pregnant (MENTION HOW LONG TO AVOID MEDS

4. **Full description of the study design, methods and procedures:** Include the type of experimental design; study procedures; sequential description of what will be asked of/done to subjects; assignment of subjects to various arms of the study if applicable; doses, frequency and route of administration of medication and other treatment if applicable; kinds of data to be collected; primary outcome measurements; and follow-up procedures. If the study involves treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls. This section (4) should generally not exceed 2 single-spaced pages using 12-point type.

***Experimental design*:** Each subject will be exposed to one of the following protocols in an exposure chamber (96 cubic feet in size):

1) NO2 protocols:
   a) Filtered air, concentrated particles, 500 ppb NO_2 with concentrated particles.
   b) Filtered air, 500 ppb NO_2, 500 ppb NO_2 with concentrated particles.
2) NO protocols:
   a) Filtered air, concentrated particles, 1000 ppb NO with concentrated particles.
   b) Filtered air, 1000 ppb NO, 1000 ppb NO with concentrated particles.

Subjects will enter the exposure chamber and sit on a recumbent bicycle ergometer. The schedule of exercise will be 15 minutes on a cycle ergometer, 15 minutes rest, and this will be repeated four times for a total exposure length of 2 hrs. Exercise intensity, ie. cycle ergometer workload, will be adjusted so that subjects will breathe at a ventilatory rate, normalized for body surface area, of approximately 25 $L/m^2 \cdot$ minute.

Exposure/Administration:

- Ambient particles in Chapel Hill air less than 2.5 μm will be concentrated up to 20 fold by a new generation serial aerosol concentrator. This differs from previous concentrators used in this facility because it is also capable of concentrating particles less than 0.1 μm. The particle concentration in the chamber will be dependent on the particle concentration of Chapel Hill air on the day of the study and thus may vary from day to day. The exposure will be terminated if particle mass inside the chamber exceeds 500 $\mu g/m^3$. The temperature and humidity of the air entering the chamber will be controlled and PM-concentrations will be measured continuously.
- **NO_2** will be added to the air stream coming from the concentrator after it was adjusted for temperature and humidity. The flow of NO_2 will be adjusted so that the concentration measured at the entry of the air

into the chamber is 500 ppb NO_2, (+/-10%). NO_2 concentrations will be measured continuously at the entry of the chamber.

Primary outcomes:

- **Bronchoalveolar lavage (BAL):** Subjects will undergo fiberoptic bronchoscopy with BAL 20 hours after each exposure. A licensed physician who is Board certified in pulmonary medicine and is experienced in the use of a fiberoptic bronchoscope will perform the procedure. Differential cell counts, cytokines (IL-6, IL-8 TNFα,), prostaglandins, fibronectin, and LDH will be measured.
- **Heart Rate Variability** will be assessed before, immediately after and 20 hrs after each exposure. After 15 minutes at rest in semi-recumbency, recording will be started: The beat-to-beat R-R intervals are recorded for 10 minutes followed by analysis of time and frequency domains. Time domain variables to be measured include SDNN and PNN50; frequency domain variables include low frequency, high frequency, and total power. In addition, abnormal beats recorded during the Holter monitor recording will be assessed
- **Peripheral venous blood** samples will be taken before each exposure, immediately after and 20 hrs after each exposure. Each time 60 cc will be drawn. The following parameters will be measured: Inflammatory and acute phase markers such as IL-6, C reactive protein and fibrinogen; and coagulation factors such as d-dimer, von-Willibrand factor, and plasminogen; and markers of endothelial cell dysfunction such as endothelins.

66.5 199.5 Total for 3 exp TOTAL 398.50 all exposures

Secondary outcomes:

- **Heart rate and SpO2** (pulse oximetry) will be monitored continuously during the exposure.
- **Lung Functions** will be measured before and after each exposure. Subjects will perform spirometry, and single breath diffusing capacity (DLCO) on a Sensor Medic Vmax pulmonary function system according to the standard algorithm published by the American Thoracic Society. In addition, regional DLCO and pulmonary capillary blood flow (Qc) will be obtained by the intrabreath technique using the same system.

5. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable**: Include the number of required visits and approximate duration of each visit.

It is anticipated that the duration of this study will be approximately one year. Subject recruitment and screening is expected to be continuous throughout the study until the intended number of subjects is reached. There will usually be about 1 to 2 exposures per week. The duration of a subject's participation during each exposure will be approximately 24 hours, including exposure, testing and bronchoscopy. The duration between exposures will be at least 4 weeks.

6. **Where will the subjects be studied?** If off UNC-CH campus, list locations.

All exposures will be carried out at the EPA Human Studies Facility on the UNC campus.

7. **Full description of risks and measures to minimize risks:** Include risk of psychosocial harm (e.g. emotional distress, embarrassment, breach of confidentiality, etc.) economic harm (e.g. loss of insurability) and legal jeopardy (e.g. disclosure of illegal activity) as well as known side effects of study medication, if applicable, and risk of pain and physical injury.

- **Pulmonary Function Tests.** These are standard non-invasive techniques that have been used in hundreds of studies and on populations of all ages and entail no risk to the subject. The intrabreath technique uses acetylene uptake for Qc measurement. Although large doses of acetylene are associated with nausea, vomiting and headache, these risks are minimal because subjects in our study are exposed to low concentrations (0.3%) for a brief period of time (single inhalation and exhalation).
- **ECG and Heart Rate Variability**. These are standard non-invasive techniques that have been used in hundreds of studies and on populations of all ages and entail no risk to the subject. However, there is the possibility that preparation of the skin for electrode placement and removal of electrodes may cause skin irritation, itching, or soreness in some people.
- **Blood sampling**. The risks associated with phlebotomy are considered minimal. Blood samples will be taken by a licensed R.N.

- **Bronchoscopy with BAL** may be associated with respiratory distress, bleeding, pneumothorax or even death. These risks are explained to the subject in full detail. Bronchoscopy procedures have been continuously performed at the Human Studies Division on the UNC-CH campus for over 10 years. During this time, more than 500 bronchoalveolar lavages have been performed without a serious incident. Established protocols for bronchoalveolar lavage and brush biopsy ensure that the safety of the subject is given absolute priority.
- **Exposure** to particles and nitrogen dioxide. The subjects in this study will be young and healthy without pre-existing cardiopulmonary disease. They will be exposed to concentrations of particles and nitrogen dioxide that do not exceed what they could encounter in a typical urban environment on a smoggy day. Subject will be exposed to concentrations of NO_2 (0.5 ppm) for two hours, which are below the current occupational threshold limit values (TLV) set for 8 hour exposures of 3 ppm. The most common symptoms associated with high level NO_2 (above 50 ppm) are sputum production, painful breathing, chest pains, cough, fever, tachycardia, lymphocytosis and increased breathing rate. These symptoms are unlikely with low level NO_2 in our study but subjects will be monitored closely and the exposure will be terminated if significant symptoms appear. Studies in tunnel workers occupationally exposed to very high levels (about TLV) of a combination of silicate dust, diesel engine particles and NO, NO_2 and CO-gases reported moderate changes in lung function after several years of exposure. Changes were attributed to continuous mild inflammation of the airways. These tunnel workers were exposed to much higher doses than used in this study. The subjects in this study will be exposed only for two hours at a time to particles or NO_2 at concentrations similar to or lower than what can be found in major metropolitan areas on smoggy days. Based on current knowledge and our previous experience, one exposure to particles, one exposure to nitrogen dioxide, and one exposure to a combination of particles and nitrogen dioxide will not have any permanent adverse health effects at the concentrations being used in this experiment. Each individual's exposures will be separated by a duration of at least 4 weeks. Currently our other ongoing bronchoscopy protocol for young normal individual uses the same interval for any given subject who wishes to return for additional bronchoscopy. Heart rate, electrocardiogram, and SpO2 by pulse oximetry will also be monitored continuously. Other indications for terminating the exposure include significant respiratory distress or dyspnea, chest or angina-like pain, significant cardiac arrhythmias, pallor, or ataxia. Subjects will be aware that they can terminate their exposure for any reason and still receive compensation for the entire exposure session. The investigator or duty physician will end the exposure if the subject is found to be suffering from any adverse effect.
- **General measures to minimize the risks**: A physician is on call whenever a subject is undergoing a procedure at the facility. A fully stocked medical station is staffed by three nurses and ~~a nurse practitioner~~, and an emergency cart, medications, and resuscitation equipment are on hand. The University of North Carolina Hospital is a short distance from the laboratory. On subsequent days after exposure, subjects will be urged to contact the Medical Station or the physician should they experience any of the following symptoms: 1) Epistaxis, 2) Persistent cough, 3) Chest pain, 4) Dyspnea, 5) Wheezing, 6) Hoarseness or sore throat.

8. **Benefits to subjects and/or society:** The possibility of benefit to society should be clearly distinguished from the possibility of benefit to the individual subject, if any. If there is no direct benefit to the individual subject, say so. Do not list monetary payment as a benefit.

To subjects: Subjects selected will receive the benefit of a complete medical examination that includes blood work, spirometry, and baseline ECG at no charge. Subjects will have full access to their records.
To society: The primary benefit to society produced by this study will be the acquisition of new information on the interactions between air pollution particles and NOx on regional lung function, inflammation and cardiovascular system. The results from this study should provide important data on adverse health effects of ambient air pollutants and their biological mechanisms that could potentially improve health of general public.

9. **Inducements for participation:** If monetary, specify the amount and how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it.

Subjects will receive monetary compensation for their time and participation at each stage of the study, including recruitment. Subjects who do not complete the study for involuntary reasons will be paid up to the part of study that they have participated. In addition, all subjects will be reimbursed for parking costs and travel expenses will be paid for subjects who live outside of Chapel Hill.

Subjects who pass the initial screen will undergo a full physical examination in the Human Studies Facility by a physician or ~~nurse practitioner~~ licensed in the State of North Carolina. As part of the physical, a blood sample (20 cc) will be obtained for an SMA-20 serum chemistry screen, and a complete blood count with differential. At this time a routine 12 lead ECG will be administered to screen the study population for baseline abnormalities including rhythm disorders (tachycardias and bradycardias), ST segment and T wave abnormalities, and arrhythmias. A cardiologist will evaluate the ECG data and significant disorders in any of the above would preclude participation in the study. Pulse oximetry will be performed at this time and if saturated oxygen levels are below 91%, subjects will be excluded from participation in the study. In addition, lung function testing will be performed to determine baseline levels of FVC, FEV1, FEF25-75, and PEF.

13. **How will informed consent be obtained?** Describe the process. When the consent of a legally authorized representative is substituted for consent of the adult subject, explain why this is necessary. If non-English-speaking subjects will be enrolled, a consent form should be prepared in their foreign language. Someone who is fluent in the subjects' language must be available to interpret.

Before being selected as subjects, all volunteers will be required to read and sign a form asserting that they have read and understood the following: 1) Subject participation is strictly voluntary, 2) The purpose of the study, 3) The nature and extent of subject participation, 4) The subject's rights to withdraw at any time, 5) The subject's right to privacy, 6) The risks associated with participation, 7) The method and schedule of compensation, and 8) The limits of the University and PI's liability.

The PI will describe the study and answer any questions that each subject might have regarding his/her participation, the safety of the procedures, issues related to payment, etc. The PI will then review the contents of the consent form before he and the subject sign it. Subjects will have the opportunity to ask questions at any time during the study by contacting one of the PIs and/or the medical staff.

The following table details the expected compensation for a subject who completes the entire study (3 exposures):

Pre-study Qualifications	
Screening	$15
Physical Exam	$15
Exposure Session (3 exposures, 2 hrs per exposure at $36/hr)	$216
Training (1hr), check-in, pre-testing and post-testing (4hrs x 3 = 12 hrs), day-after-exposure testing (2hr x 3 = 6 hrs) at $12/hr	$228
Pulmonary function tests with DLCO (at $40 each x 6)	$240
24 hour holter monitor (at $100 each x 3)	$300
Bronchoscopy with lavage and recovery (at $325 each x 3)	$1075
Completion bonus	$50
Total Compensation	**$2139**

10. **Costs to be borne by subjects:** Include clinic fees, diagnostic and laboratory studies, drugs, devices, transportation, all professional fees, etc. If there are no costs to subjects, indicate this.

Subjects will not be responsible for any of the costs incurred during their participation in the study. Reimbursement will be made for parking charges and transportation costs for subjects who live outside of Chapel Hill.

11. **Statistical analysis:** If this is a single-center clinical trial, provide evidence that the sample size is sufficient to achieve the study aims and tell how the data will be analyzed. If a multicenter trial, indicate where and by whom statistical analysis will be performed.

The hypothesis to be tested is that a combination of nitrogen oxides and ambient particles will affect regional lung function and heart rate variability more than particles alone. In addition a number of exploratory hypotheses concerning the release of inflammatory and vasoactive mediators will be examined. Statistical data analyses will consist of analysis of variance followed by Tukey's test to determine differences between groups. The minimal sample size necessary to detect a difference of 10% between PM effects and combined effects (PM*NO or PM*NO_2) at an alpha of 0.05 and a power of 0.8 is n=15 per exposure group based on paired design. A number of 20 subjects per group (80 in total) will be needed to account for unsuccessful trials and for subjects who do not complete all three exposure sessions.

12. **Methods of recruiting:** Tell how prospective subjects are contacted. If they are UNC Hospital patients, initial contact should be made by their treating physician, or by someone whom the patients know to have legitimate access to their medical records (for example, a clinical director). This may be accomplished by means of a letter from that individual to prospective subjects, requesting the patient's permission to be contacted by the investigator.

Subjects will be recruited for this study by the Westat Corporation, which has recruited subjects for studies at the Human Studies Facility since 1998. The manner in which this will be done is identical to that of past EPA studies and specific recruitment procedures are described in the subject recruitment protocol on file with the UNC Committee for the Protection of the Rights of Human Subjects. The population targeted will be young healthy residents of the Triangle area. Every effort will be made to recruit women and members of ethnic minority groups into this study. Advertisements will be placed in local newspapers, around university campuses, and in publications targeting to young adults. Volunteers will be asked to call the recruitment office. During the telephone interview, the volunteers will receive information regarding the study and their eligibility status will be assessed. Volunteers whose responses indicate that they are likely to meet the criteria will be scheduled for an appointment in the Westat recruitment office in the Human Studies Facility. At that time the entire study protocol will be outlined, and a medical history form and ~~(Minnesota Multiphasic inventory (MMPI) will be administered.) The MMPI will be scored on all twelve scales and subjects may be excluded if they are out of range on any scale: this may identify personality types who may be adversely affected by participation in research studies or in enclosed exposure chambers~~. The medical history form records complete information on general personal and family medical history.